

one of ordinary skill in the art would develop an art recognized animal model and correlate to human utility for potential therapeutic agent which eventually intended for human application. Therefore, one of ordinary skill in the art would have been motivated to develop or use the already established data of Morrow et al. for the *in vivo* efficacy of the instantly claimed invention. (Paper No. 9, p. 4)

Morrow et al. disclose that prostaglandin F₂-like compounds can be generated *in vitro* in plasma in two ways. First, the prostaglandin F₂-like compounds can be generated by prolonged storage of plasma at -20°C. Second, the prostaglandin F₂-like compounds can be generated by repeatedly freezing and thawing plasma. Morrow et al. determined that the prostaglandin F₂-like compounds were formed by a non-cyclooxygenase mechanism via autoxidation of arachidonic acid contained in the plasma.

Applicants' invention claims a method for assessing oxidative stress *in vivo* by quantification of prostaglandin F₂-like compounds. Applicants discovered that high levels of prostaglandin F₂-like compounds were produced *in vivo* in response to agents that cause free radical induced lipid peroxidation. This finding has fulfilled a great need in the art -- the development of an assay to determine oxidative stress *in vivo* by the quantification of these prostaglandin-like compounds.

Applicants' disagree with the Examiner's argument in the March 22, 1993 final Office Action cited above. The Examiner's argument refers to the development of an animal model to test a therapeutic agent for potential human application. While this argument may be true with respect to therapeutic agents, this

argument is not applicable as to whether a particular chemical process demonstrated to occur *in vitro* in a test tube also occurs in the body of humans or other animals. With most chemical processes discovered *in vitro* there is nothing to suggest that the discovered process has relevance to biological chemistry or biological processes. The development of a drug for therapeutic use in humans always involves testing the drug in an acceptable animal model. However, this has nothing to do with attempting to discover whether a certain chemical process, as the Applicants discovered initially to occur during storage of plasma in the freezer, also occurs in the body.

Morrow et al. showed that prostaglandin F_2 -like compounds could be generated *in vitro* by autoxidation during prolonged storage of plasma at -20°C or in plasma that had been repeatedly frozen and thawed. There was nothing in this reference to suggest to one skilled in the art that this finding was more than test-tube chemistry. There was nothing in this reference that suggested or taught any relevance of this chemistry to biological chemistry or biological processes. Finally, the Morrow et al. reference was published in an "Analytical" journal and the sole point of the article was to alert other scientists that prostaglandins can be generated during storage of biological samples which could lead to artifactual results when stored samples are analyzed for prostaglandins.

Applicants have supplied a 132 declaration of Dr. Lawrence Marnett who has been actively involved in research in the area of

prostaglandins and free radicals for over 20 years. Dr. Marnett states that the discovery by the Applicants that prostaglandin F₂-like compounds were produced *in vivo* was surprising because it demonstrated that compounds related to prostaglandins could be formed chemically instead of enzymatically. See Marnett declaration of paragraph 4. Dr. Marnett also states that prior to the Applicants' discovery, there was no convincing evidence that free radical-catalyzed peroxidation of lipids actually occurred *in vivo*. See Marnett declaration at paragraph 5. According to Dr. Marnett, Applicants provided the first convincing evidence that peroxidation occurred *in vivo* and this finding was surprising to the scientific community. Id.

Obviousness is tested by what the combined teachings of the references would have suggested to one of ordinary skill in the art. Ex parte Kranz, 19 USPQ 2d 1216, 1218 (1991). Before obviousness can be established, the Examiner must show that there is a suggestion in the art to produce the claimed invention of a compelling motivation based on sound scientific principles. Id.

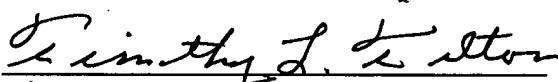
In this case, the Examiner has noted that art teaches that certain prostaglandin F₂-like compounds could be produced *in vitro* by autoxidation during prolonged storage of plasma at -20°C. As stated by the Applicants earlier, this finding was simply test tube chemistry. However, the art fails to provide any suggestion or teaching that this same chemistry and prostaglandin F₂-like compounds could be produced *in vivo*. In fact, the art fails to

teach that lipid peroxidation, the mechanism by which these compounds are produced *in vivo*, even occurred in the human body. Additionally, the art fails to suggest that these same compounds could be used to measure oxidative stress *in vivo* by measuring the level of these prostaglandin F₂-like compounds in fresh biological fluid and comparing them with a control.

Conclusion

Based upon the above arguments and the affidavit of Dr. Marnett, Applicants submit that the claims are now in condition for allowance. If any fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 20-1111.

Respectfully submitted,


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